# CIRM Statement: First Clinical Trial Begins for a Therapy Enabled By CIRM Funding

Posted: April 8, 2008

Researchers at the University of California, San Diego, used a training grant and a seed grant from the California Institute for Regenerative Medicine to conduct stem-cell research that verified a suspect gene mutation was by itself necessary and sufficient to cause a class of severe blood diseases called myeloproliferative disorders. They then worked with a team of researchers from other academic institutions and from the San Diego pharmaceutical company TargeGen to conduct animal tests of a compound TargeGen had already isolated and shown to inhibit that same genetic pathway. As a result of this broad collaboration, human clinical trials for this potential therapy began in February.

"Our grants review committee was able to award this grant in February 2007,while our bond authority was delayed by litigation, because of the assurance of funding provided by Governor Schwarzenegger authorizing up to $150 million in loans to CIRM the previous August," said Robert Klein, chair of the CIRM Independent Citizens Oversight Committee.The more than 100,000 Americans with these blood disorders, which are severely debilitating and can lead to leukemia, thank the Governor for advancing the CIRM model designed to accelerate the quest for cures. The governor's intervention has provided the opportunity to reduce the pain and suffering of tens of thousands of patients and their families."

The press release from UCSD is below.

**From Bench to Bedside in One Year: Stem Cell Research Leads to Potential New Therapy for Rare Blood Disorder**

A unique partnership between industry and academia has led to human clinical trials of a new drug for a rare class of blood diseases called myeloproliferative disorders (MPD), which are all driven by the same genetic mutation and can evolve into leukemia. In just one year, collaborative discoveries by stem cell researchers from the University of California, San Diego, Dana-Farber Cancer Institute, the Mayo Clinic and a San Diego pharmaceutical company, TargeGen, moved from identification of the most promising drug candidate to clinical trials for a new drug to fight this degenerative blood disorder, which affects more than 100,000 Americans.

A study headed by Catriona H.M. Jamieson, M.D. Ph.D., assistant professor of medicine at the University of California, San Diego and Director for Stem Cell Research at Moores UCSD Cancer Center, found an inhibitor that can stop the over-proliferation of blood cells that results in problems with blood clotting, heart attacks and, in some cases, leukemia. Funded in part by a grant from the California Institute for Regenerative Medicine (CIRM), the study will be published in *Cancer Cell* on April 8, 2008. A parallel study at Harvard Medical School, headed by D. Gary Gilliland, Ph.D., M.D., yielded similar results which will appear in the same issue of *Cancer Cell*.

"As a clinician, I asked myself who is going to get this disease, and what can we do to stop its progression, instead of waiting until it evolves into a deadly cancer?" said Jamieson. "This project has been so extraordinary, because a small pharmaceutical company took a big chance on a rare disease."

With major contributions from collaborators Jason Gotlib at Stanford University and Ayalew Tefferi at the Mayo Clinic, the research findings led to development of the inhibitor by TargeGen. That drug is currently being tested in human clinical trials at the UC San Diego School of Medicine, the Mayo Clinic, M.D. Anderson Cancer Center, and the University of Michigan, Stanford and Harvard University Schools of Medicine.

A patient with MPD makes too many blood cells, caused by a mutation expressed in the stem cell, the early stage cell that goes on to differentiate to become either red or white blood cells. In 2006, Jamieson was first author on a paper published in *PNAS* , outlining the discovery that a mutation in the JAK2signaling pathway in patients with a type of MPD called *polycythemia vera* (PV) allows cells to bypass the process which would normally regulate the production of red blood cells. As a result of this defect, the bone marrow produces excessive numbers of red blood cells.

In the current research described in *Cancer Cell*, the UCSD School of Medicine researchers and collaborators transferred human cord blood stem cells, engineered to contain the mutant JAK2 gene, into mouse models with a suppressed immune system to find whether over-expression of a single gene could drive, or initiate, the disease. These stem cells were introduced directly into the liver, the main site of blood development in the newborn mouse. As a result, the stem cells over-expressing the mutant gene led to overproduction of human red blood cells, and the mice developed a disease that looked like PV.

The researchers corroborated these results by injecting actual stem cells from patients with PV into the same mouse model, achieving similar results. "We found that the JAK2 mutation was necessary and sufficient, by itself, to drive the disease," Jamieson said.

Theorizing that blocking this mutation would prevent overproduction of red blood cells, TargeGen developed a selective JAK2 inhibitor called TG101348. This therapy was shown in animal studies to halt over-expression of the gene and reverse excessive production of red blood cells. Because TG101348 selectively targets the JAK2 protein that causes the disease, side effects have been minimized.

“Pre-clinical testing at the UCSD and Harvard University Schools of Medicine confirmed the therapeutic potential of TG101348. The compound was rapidly advanced into the current, ongoing human clinical trials being conducted at major research institutions across the country,” said John Hood, Ph.D., Director of Research for TargeGen. “This unique industry-academia collaboration has helped guide a new drug from bench to bedside, from evaluating the compound’s efficacy on cancer stem cells to its evaluation in patients bearing a disease which otherwise has very limited treatment options.”

Under the auspices of Jamieson, co-first authors Ifat Geron, M.S., and Annelie Abrahamsson, M.S., worked in close collaboration with Kenneth Kaushansky, M.D., chair of the UCSD Department of Medicine; Jason Gotlib, M.D., M.S., at Stanford University School of Medicine; and Ayalew Tefferi, M.D., Department of Medicine at the Mayo Clinic in Minnesota.

Additional contributors to this study include Charlene Barroga, Ph.D. and Edward Kavalerchik, M.D., UCSD Department of Medicine; John Hood, Ph.D., Chi Ching Mak, Glenn Noronha and Richard Soll, Ph.D., TargeGen Inc., San Diego; and Jeffrey Durocher, PH.D., Transgenomic Inc., Gaithersberg, MD.The study was funded in part by the California Institute for Regenerative Medicine and the Mizrahi Family Foundation, the National Institutes of Health (K23HL04409) and an unrestricted gift from TargeGen Inc.

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